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October 18, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

8ECAP

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
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ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not.exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

- othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g,* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

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[6] 43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112

"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS: 2431-50-7
Chem:Trichlorobutene
Title: Effect of 2,3,4-trichlorobutene-1 inhalation on pregnancy of the rat
Date: 7/78
Summary of Effects: Decrease in fetal body weight at the high exposure level (2.5 ppm)

3339

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Utrechtseweg 48
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CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH

REPORT NO. R 5748

Effect of 2, 3, 4 - trichlorobutene - 1 inhalation on pregnancy of the rat

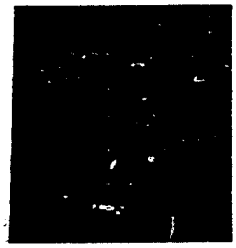
Authors: H. B. W. M. Koëter
Drs. P. G. J. Reuzel

At the request of: The Joint Industry Committee on Chloroprene

Project number: B77 - 1103

Approved by: Dr. A. P. de Groot

Date: July, 1978



SUMMARY.

1. Pregnant rats were exposed to atmospheres containing respectively 0.0(control), 0.1, 0.5 or 2.5 ppm 2, 3, 4-trichlorobutene-1 for 6 hours/day from day 6 - 16 of gestation.

2. Diminished food consumption and weight gain during treatment and post-treatment occurred at 2.5 ppm.

3. Mean foetal and mean placental weights were decreased at 2.5 ppm.

4. Skeletal and visceral examination of foetuses revealed no malformations, attributable to the exposure to the test compound.

5. On the basis of maternal and foetal growth depression, 2.5 ppm 2, 3, 4-trichlorobutene-1 is considered to be slightly toxic when exposed to pregnant rats.
The exposure to 2, 3, 4-trichlorobutene-1 at various levels up to and including 2.5 ppm did not exert any teratogenic effect on rat foetuses.

Effect of 2, 3, 4-trichlorobutene-1 inhalation on pregnancy of the rat.

1. INTRODUCTION

At the request of the Joint Industry Committee on Chloroprene, the embryo-toxicity and foeto-toxicity of 2, 3, 4-trichlorobutene-1 (TCB), was tested in pregnant rats, which were exposed to test atmospheres. containing 0, 0.1, 0.5 or 2.5 ppm of the test compound. The rats were exposed for six hours a day during the period of organogenesis..

In this study, general appearance, growth, food intake, ovary and uterus weights, numbers of corpora lutea and implantation sites, foetal and placental weights, and gross examination as well as skeletal and soft tissue defects of the foetuses were used as criteria to disclose possible harmful effects.

2. PROCEDURE

2.1 Material and methods

Six bottles each containing 100 ml freshly purified 2, 3, 4-trichlorobutene-1 (TCB), were received weekly from Bayer AG. Dormagen, W-Germany, and stored at 21 ^{o} C.

To generate the various test atmospheres, suitable quantities of the test material were put into glass fritted, glass bubble evaporators, kept at room temperature, through which a measured, dried and filtered nitrogen flow was passed. Each of the TCB / nitrogen mixtures thus produced, were led into the inlet piece of a 2.5 m^3 stainless steel / glass inhalation chamber, where it was mixed with the main air flow of 40 m^3/h. Teflon and stainless steel transport tubes were used. The temperature inside the exposure chambers was 23 $\pm$ 2 ^{o} C, the relative humidity was 45 - 65 %.

Air samples were taken from each inhalation chamber during the exposure (average three samples/hour) by means of a sample loop and then injected into a gas-chromatograph. Two gas chromatographs were used, one, an Intersmat IGL-DFL, was fitted with a flame ionisation detector, the other, an Intersmat GC, was fitted with an electron attachment detector with a Ni 63 source. The following operating conditions were established:

		IGL-DFL	GC
Column		150 x 4 mm	packed with from S/25%LAC
Temperature	a. Injectionport	100 °C	150 °C
	b. Oven	135 °C	135 °C
	c. Detector	150 °C	280 °C

The gaschromatographs were calibrated by injecting 1µl of a calculated solution of TCB in a solvent. The sample loop was calibrated by comparing peak surfaces of samples taken with a gas-tight syringe with peak surfaces of simultaniously taken loop-samples.

2.2 Animals

Adult male and virgin female albino rats from the Wistar strain, bred under SPF conditions at the Central Institute for the Breeding of Laboratory Animals TNO, Zeist, The Netherlands, were used. The animals were individually housed in a room controlled for light, temperature and humidity. They were conditioned for one week prior to use.

2.3 Conduct of the experiment

Four groups of twenty-three females were mated with males (two females were caged with one male) to obtain a sufficient number of pregnant rats. Vaginal smears were taken daily to determine whether mating had occurred. The day of detection of spermatozoa was considered as day 0 of pregnancy. The pregnant females were individually housed in suspended, screen bottomed stainless steel cages until day 6 and from day 16 to day 21 of pregnancy. The Institute's stock diet and tap water were available ad libitum during these periods. During the period of organogenesis (day 6 to day 16 of pregnancy) the females were exposed to the test atmospheres for 6 hours/day. For that purpose each group was housed in a stainless steel/glass inhalation chamber in wire-mesh cages; one animal per cage. The cages were suspended in a hexagonal frame, rotatable around the vertical axis of the chamber. The position of the cages in the chamber was changed daily according to a fixed scheme. During the exposures the animals had no access to food and water. In the non-exposure periods the animals remained in the inhalation chambers; stock diet and tap water was then available ad libitum.

The dams were weighed individually on the day after mating (day 0) and on days 6, 16 and 21. Food consumption was determined individually during the following periods: day 0-6, day 6-16 and day 16-21.
On day 21 of pregnancy the dams were killed by decapitation. Both ovaries and the uterus were removed. The number of corpora lutea of pregnancy in each ovary was recorded and both ovaries were weighed. The foetuses were removed from the uterus, dried of amniotic fluid, weighed and examined for gross abnormalities. The placentas of the live foetuses were weighed and intra-uterine dead embryos and foetuses were counted and the number and position of all implantation sites in both uterine horns was recorded. The empty uterus was then weighed.
One third of the number of foetuses of each litter was fixed in 96% ethanol after having been eviscerated, skinned and stripped of most subcutaneous tissue. Thereafter these foetuses were cleared and stained with Alizarin Red S for examination of the skeleton. The remaining foetuses were fixed in Bouin's fluid, then transferred to 70% ethanol before being cut into a number of slices according to the technique of Wilson (1965) for examination of the soft tissues.
All examinations for foetal abnormalities were carried out under a dissecting microscope. Skeletal examination was carried out on the foetuses of all groups while soft tissue examination was restricted to the foetuses of the highest dose group and the controls.

2.4 Calculations and statistics

Resorption sites were classified as "embryonic" when only the placenta was visible and "foetal" when both placental and embryonic tissue was visible at termination. For each litter pre-implantation loss was calculated as a percentage from the formula:

$$\frac{\text{no. of corpora lutea} - \text{no. of implantation sites}}{\text{no. of corpora lutea}} \times 100$$

Post implantation loss was similarly calculated from the formula:

$$\frac{\text{no. of implantation sites} - \text{no. of live young}}{\text{no. of implantation sites}} \times 100$$

For statistical analyses of the bodyweights, food consumption, organ weights and litter data, Student's t-test was applied.

Skeletal and visceral anomalies were evaluated by the Chi-square test. For the statistical analyses of variations in ossification in foetal skeletons, Student's t-test was applied on values per litter, expressed in degrees, which were calculated from the formula:

$$\text{arcsinus } \sqrt{\frac{\text{number of bones with absent or incomplete ossification}}{\text{number of bones examined}}}$$

3. RESULTS

3.1 Concentrations of TCB in the atmospheres

Within a period of 25 consecutive days (a mating period of 16 days and 9 days of exposing the last mated females) all females were exposed. The mean concentrations during this period are presented in table 1.

3.2 General appearance and pregnancy rate.

Although as many as twenty three females in the control group and in each dose group showed successful matings, the number of pregnancies turned out to vary between 17 and 21.This pregnancy rate, however is well within the normal range (c.f. appendix 1).
During the experiment no deaths occurred and no abnormalities of condition or behaviour were observed.

3.3 Growth and food intake

Mean maternal bodyweights, weight gain and foodintake figures of dams with live young, are given in table 2. Maternal bodyweights and food consumption were significantly decreased during the treatment and post-treatment period in the highest dose group.

3.4 Autopsy findings, organ weights and litter data

Maternal and autopsy findings, organ weights and litter data are presented in table 3. Pre-implantation loss was increased in the 0. ppm dose group only. Since no dose relationship was observed and since moreover this higher value was within the range as observed
in control series, (c.f.appendix 2) no toxicological significance is attached to this finding.

Foetal and placental weights were decreased in the highest dose group. The other parameters were comparable in all groups. Upon macroscopic examination of the litters, no malformed foetuses were found in any of the test groups.

3.5 Examination of the foetal soft tissues

Type and incidence of visceral anomalies are listed in table 4, expressed in numbers of foetuses and numbers of affected litters. One foetus of the control group showed a major malformation, consisting of a partially cleft palate. Two foetuses of the highest dose group showed unilateral agenesis of the testis. Although not observed in the control group, this finding is not uncommon in the strain of rats used. The other observations listed in the table were minor anomalies and occurred in the controls as well as in the highest dose group or occurred only in a single foetus. No foetal soft tissue malformations were observed that could be related to treatment.

3.6 Examination of the foetal skeletons

Examination of the foetal skeletons did not reveal any major abnormalities. Only minor anomalies, such as dislocated sternebrae, separated sternal ossification points or a unilateral missing 13th rib were observed. The distribution of these anomalies was about equal in test and control groups. Variations in ossification of foetal skeletons are given in table 5. Significant differences occurred in the ossification of metatarsals, hindlimb phalanges and cervical vertebral bodies. Since increased as well as decreased degrees of ossification were observed and since, moreover all values were comparable with mean values as observed in control series, they are considered to reflect the normal variation in ossification of foetal skeletons in the strain of rats used.

DISCUSSION AND CONCLUSIONS

The exposure of rats to test atmospheres containing 0.1, 0.5 or 2.5 ppm 2, 3, 4-trichlorobutene-1 (TCB) during day 6 - 16 of pregnancy was accompanied by a decrease in food consumption and bodyweights during the treatment and post-treatment period in animals of the highest dose group.

Therefore, the exposure of 2.5 ppm is considered to be slightly toxic to pregnant rats.
Mean foetal and mean placental weights were decreased at the highest level. However, no dead foetuses occurred and no increase in post-implantations was observed. In addition neither skeletal nor visceral examination of foetuses revealed any malformations that could be related to treatment. From the present results it is therefore concluded that the exposure of rats to test atmospheres, containing 0.1, 0.5 or 2.5 ppm TCB during day 6 - 16 of pregnancy induced some foetal growth depression at the 2.5 ppm level but did not exert any teratogenic effect on rat foetuses.

5. REFERENCES

Wilson, J. G., Embryological considerations in teratology.
In "Teratology, principles and techniques". Ed. by J.G. Wilson and J. Warkany, University of Chicago Press, Chicago, Illinois, 1965.

CIVO-TNO/vdH
21-7-1978

Table 1.

Mean concentrations of TCB in the test atmosphere during an exposure period of 25 days.

	Concentration of TCB in ppm			
Group no	1	2	3	4
nominal	0	0.10	0.50	2.50
actual	-	0.10	0.44	2.54
standard deviation	-	0.01	0.13	0.39
standard error of the mean	-	0.00	0.02	0.08

Table 2.

Mean maternal body weights, weight-gain and food intake of dams with live young.

ppm TCB by inhalation	number of dams examined	mean maternal body weight (g) at day 0	6	16	21	weight gain (g) during treatment	weight gain (g) during gestation	mean food intake g/rat/day from day: 0-6	6-16	16-21
0	17	175	196	228	276	32	101	14.7	15.8	17.7
0.1	21	175	195	229	273	34	100	14.7	16.2	16.7
0.5	19	172	191	221	267	30	95	14.4	15.5	16.7
2.5	17	172	193	196***	235***	3***	63***	14.4	9.8***	15.5*

* 0.05 >p >0.01

*** p <0.001

Table 3.

Maternal and autopsy findings, organ weights and litter data.

parameter	ppm TCB dosed by inhalation: 0			0.1			0.5			t
	total	mean	range	total	mean	range	total	mean	range	
number of females mated	23			23			23			
number of females pregnant	17			21			19			
number of females with live foetuses	17			21			19			
number of live foetuses	177	10.4	7-13	224	10.7	7-14	185	9.7	5-14	17
number of litters with externally visible malformed foetuses	0			0			0			
number of foetuses with externally visible malformations	0			0			0			
number of foetuses prepared for skeletal examination	53			66			56			5
number of foetuses prepared for visceral examination	123			158			129			12
pre-implantation loss (%)		3.48	0.-9.09		4.78	0-21.43		14.61*	0-54.55	
post-implantation loss (%)		3.43	0-11.11		5.37	0-30.0		3.72	0-25.0	
ovary weight (mg)		82.2	66.0-99.5		82.9	62.0-106.0		82.1	58.5-104.0	
empty uterus weight (g)		4.01	3.09-5.58		4.33	2.83-5.95		3.82	2.18-5.56	
number of corpora lutea	190	11.2	7-13	249	11.9	10-14	226	11.9	11-15	198
number of implantation sites	183	10.8	7-12	236	11.2	11-14	193	10.2	5-14	181
number of embryonic resorptions	4	0.24	0-1	8	0.38	0-2	6	0.32	0-3	3
number of foetal resorptions	2	0.12	0-1	4	0.19	0-2	2	0.11	0-1	1
foetal weight (g)		4.66	4.08-4.98		4.71	3.46-5.06		4.71	4.04-5.16	
placental weight (g)		0.54	0.47-0.61		0.54	0.48-0.69		0.55	0.44-0.69	

* $0.05 > p > 0.01$

** $0.01 > p > 0$

Table 4.

Type and incidence of visceral anomalies (foetuses/litters).

Parameter	ppm TCR dosed by inhalation	
	0	2.5
number of litters examined	17	17
number of foetuses examined	116	119
number of litters with one foetus showing visceral anomalies	10	4
number of litters with more than one foetus showing visceral anomalies	2	0
total number of foetuses with visceral anomalies	14	4
palate		
partially cleft	1/1	0/0
kidney		
slightly increased pelvic cavitation		
a. unilateral	3/3	0/0
b. bilateral	8/8	1/1
thyroid		
unilateral hypotrophy	0/0	1/1
testis		
unilateral agenesis	0/0	2/2
abdomen		
filled with haemorrhagic fluid	1/1	0/0
extremities		
s[illegible]ure of left forelimb	1/1	0/0
skin		
subcutaneous haemorrhage	1/1	0/0

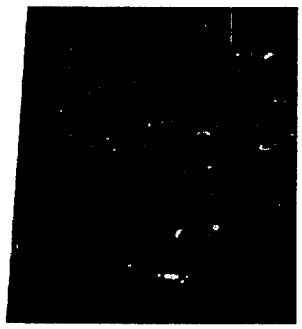


Table 5.

Variation in ossification of foetal skeletons expressed as transformed percentages.')

Parameter	ppm TCB dosed by inhalation			
	0	0.1	0.5	2.5
number of litters examined	17	21	19	17
ossification absent				
forelimb: metacarpals	26.55	26.38	25.82	26.56
phalanges	40.84	44.54	43.99	43.52
hindlimb: metatarsals	7.39	5.69	7.11	10.54
phalanges	46.85	50.09	51.45*	51.48*
cervical vertebral bodies	23.49	20.83	28.90	28.50
ossification incomplete				
forelimb: metacarpals	26.76	26.60	26.03	26.56
phalanges	23.44	21.86	22.45	21.29
hindlimb: metatarsals	26.06	24.99	21.96	20.31*
phalanges	18.05	12.23*	13.17	11.31
cervical vertebral bodies	11.27	7.02	4.82	0.74**

* $0.05 > P > 0.01$

** $0.01 > P > 0.001$

')transformation is described in point 2.4 page 3.

Appendix 1.

Summary of maternal findings and malformed foetuses in control series.
Derived from: 246 dams
2491 foetuses

PARAMETER	total	percentage		
		mean	range ')	
			low	high
number of females mated	294			
number of females pregnant	246	83.7	60	100
number of pregnant females with live foetuses	245	99.6	94.4	100
number of litters with externally visible malformed foetuses	7	2.9	0	20
number of foetuses with externally visible malformations	7	0.3	0	1.5

') Low range: Lowest mean value as observed in a control serie
High range: Highest mean value as observed in a control serie

Appendix 2.

Summary of litter data and organ weights
Derived from: 246 dams
2491 foetuses

PARAMETER	mean	range ') low	range ') high
number of live foetuses-litter	9.8	8.0	13.0
ovary weight (g)	0.09	0.06	0.12
empty uterus weight (g)	4.02	2.86	5.30
number of corpora lutea-dam	11.8	10.0	14.6
number of implantation sites-dam	10.1	8.9	14.0
number of embryonic resorptions-dam	0.48	0.0	1.66
number of foetal resorptions-dam	0.04	0.0	0.22
number of dead foetuses-dam	0.03	0.0	0.11
foetal weight-litter (g)	4.88	3.61	5.33
pre-implantation loss %	8.3	3.0	19.2
post-implantation loss %	6.1	2.0	17.2

') low range : lowest mean value as observed in a control serie
high range : highest mean value as observed in a control serie

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

Submission number: 13154A

NON-CAP (CAP)

TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI (RTOX) GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: (0) 1 2 **pages** 1, 1st tab **pages** 1, all tabs.

Notes:

Contractor reviewer : LPS **Date:** 5/11/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1092 -13154 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

SUB. DATE: 10/18/92 OTS DATE: 11/02/92 CSRAD DATE: 03/23/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER ROUTES
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
2431-50-7

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	01 (02) 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	(LOW - Mod)		
CAS SR	NO	NO (CONTINUE)		MED		
	UNKNOWN	REFER		HIGH		

COMMENTS

Developmental, rat via inhalation
0, 0.1, 0.5, 2.5 ppm 6 hrs/day GD 6-16

only effects observed at high dose of 2.5 ppm:
- ↓ food consump., maternal weight gain
- ↓ mean fetal + placental weights

no skeletal, visceral malformations at any dose level.